An Improved Approach to Developing Uncertainty Factors for the Inhalation Risk of Chloroform

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Chloroform is a drinking water disinfectant byproduct and is a potential health concern because excess exposure damages the liver and kidney. Exposure from drinking water occurs via the oral, dermal, and inhalation routes. Oxidative metabolism of chloroform in the liver is catalyzed by cytochrome P450 2E1 (CYP2E1) and produces phosgene and HCl which, at high concentrations, lead to cytolethality, subsequent cell proliferation or hyperplasia, and cancer; chloroform is not carcinogenic in the absence of cytolethality. The content of CYP2E1 varies among humans, influenced by ethanol ingestion, stress, fasting, genetics, and diabetes. The delivery of chloroform to the liver by hepatic blood flow is also a determinant of metabolism; hepatic blood flow varies among humans. For systemic toxicity, data from rodent studies indicate that 5 ppm may be a safe exposure level. While rodents develop nasal toxicity at lower concentrations, the effect is not seen in humans, and species differences in the distribution of enzymes to nasal tissues may be partly responsible. Chloroform's reference concentration (RfC) will be developed based on systemic effects, and the approach employs physiologically based pharmacokinetic modeling to transition concentrations of chloroform in inspired air to the amount of metabolite formed in the liver of adults and children. The model is improved over predecessors by including measures of variability in CYP2E1 content derived from human adult and child organ donor tissues, the biochemically measured specific activity of human CYP2E1 toward chloroform, clinically derived measures of variability in hepatic blood flow (% of cardiac output) among humans, and the blood:air partition coefficients derived from human adult and child blood. The results quantify animal-to-human and human interindividual variations in the amount of chloroform metabolized in the liver. These differences represent a more scientifically sound basis for uncertainty factors than default assumptions.

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